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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,104	BARSKY ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003 and 16 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,28,29 and 50-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,28,29 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 7, 2003 has been entered. Claims 1, 5, 12, and 28 have been amended. Claims 13-27 have been cancelled. Claims 50-52 have been newly added.

Accordingly, Claims 1-12, 28, 29, and 50-52 remain pending in the instant application.

Drawings

The drawings are objected to because features referred to in the specification are not visible in the drawings. The drawings in the application file are in black and white, but the specification refers to color drawings. For example, the legend to Figure 3 (page 5, lines 20-22) refers to a "strong yellow-orange fluorescence ... depicted in the cell population at the lower portion of the slide (E)." The features referred to are not visible because the photograph is in black and white.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied. The Office will accept color drawings and/or color photographs in utility applications only after granting a petition filed under 37 CFR 1.84(a)(2). Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three (3) sets of color drawings or color photographs, as appropriate, a black and white photocopy, that accurately depicts, to the extent possible, the subject matter shown in the color drawing, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a product of nature, which is non-statutory subject matter.

Claims 1-5 are directed to a human inflammatory breast cancer (IBC) xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host and comprises certain claim-designated properties.

The term xenograft is given its broadest reasonable interpretation. As such, the term covers the graft material alone prior to introduction into an animal. Thus, the term covers the IBC cell line disclosed in the instant specification, designated MARY-X. As indicated in the specification, the cell line MARY-X is a product of nature. The specification states that the MARY-X cell line was isolated from a 45 year old female (page 56, lines 6-7). The specification routinely refers to the MARY-X "xenograft" even when referring to the original graft material (i.e., the cell line) that has not yet been passaged through an animal. For example, at page 12, lines 13-16, the specification states "[i]n a highly preferred embodiment the xenograft is the human inflammatory breast cancer xenograft referred to as MARY-X (deposited with the American Type Culture Collection ... and assigned ATCC Patent Deposit No. PTA-2737)." However, it appears that the material on deposit is the cell line itself rather than tumor material passaged through an animal. There is no indication that the material on deposit was passaged through an animal and then resected. The limitation "wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host" appears to refer to a capability of the xenograft, rather than indicating that the claimed xenograft is actually located within a host animal.

This rejection may be overcome by amending the claims to recite an "isolated" cell, cell line, or xenograft. Applicant is reminded to point to appropriate support in the as-filed specificaton for any such amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-12, 28, 29, and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) a human inflammatory breast cancer (IBC) xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised **mouse**, (ii) a **mouse** model for IBC comprising an immunocompromised **mouse** which itself comprises a human inflammatory breast cancer xenograft, wherein the xenograft is present within lymphatic and blood vessel channels and has the claim-designated properties (see Claim 10), (iii) an *in vitro* culture of a human IBC cell line, wherein the cell line grows as a spheroid and has the claim-designated properties (see Claim 6), (iv) a method of generating the xenograft set forth in part (i) by implanting appropriate cells into an immunocompromised **mouse**, and (v) a method of identifying a molecule whose expression is modulated in IBC, wherein the method involves using a human IBC xenograft that grows within lymphatic and blood vessel channels of an immunocompromised **mouse**, does not reasonably provide enablement for the use of an immunocompromised host animal other than a mouse in generating the claimed animal model or propagating the claimed xenograft. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Nature of the invention and breadth of the claims. Claims 1-5 are directed to a human inflammatory breast cancer (IBC) xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host and comprises the following properties: (i) does not express estrogen receptor and progesterone receptor; and (ii) expresses p53, EGFR, MUC1, and E-cadherin. Claims 6-8 and 50 are directed to an *in vitro* culture of a human IBC xenograft, wherein the xenograft grows as a spheroid and has a specific phenotype. Claim 9 is directed to a method of making the xenograft of Claim 1. Claims 10-12 and 51 are directed to a nonhuman animal model for IBC comprising an immunocompromised host animal inoculated with a human IBC xenograft, wherein the xenograft grows within lymphatic and blood vessel channels and has a specific phenotype. Claims 28, 29 and 52 are directed to a method of identifying a molecule whose expression is modulated in IBC. Claims 28, 29, and 52 encompass both *in vitro* and *in vivo* applications of the claimed method.

The term xenograft is given its broadest reasonable interpretation. As such, the term covers the graft material alone prior to introduction into an animal. Thus, the term covers the IBC cell line disclosed in the instant specification, designated MARY-X. The term also encompasses the tumor residing in an animal once the cell line is implanted into the animal and allowed to grow. The term also encompasses the resected tumor, passaged through an animal and then removed. After passage through an animal, said xenograft may contain both human and host animal tissue.

The claims cover the use of any immunocompromised host animal, including sheep, pig, and nonhuman primates. Furthermore, the claims cover orthotopic as well as heterotopic transplantation of graft material.

Amount of direction or guidance presented and presence or absence of working examples.

In Example 3, the specification teaches the subcutaneous implantation of cells of the MARY-X cell line into both athymic nude mice and SCID mice (page 68, paragraph 2). At page 72, lines 9-11, the specification reveals that the subcutaneous injections were into the ventrolateral flanks and that the tumors were allowed to grow to 1.0 cm in diameter. The specification further discloses that MARY-X

induced erythema in the mouse skin overlying the tumors, mimicking the clinical presentation of inflammatory carcinoma (page 68, lines 22-23). MARY-X grows exclusively within murine lymphatic and blood vessel channels (page 68, lines 24-25 and Figures 1B, 1C, and 1D). Pulmonary metastases were observed, but these metastases were confined to within vessels (page 68, lines 29-31). No extravasation occurred. According to the specification, the phenotype of MARY-X is limited to intravasation (sentence bridging pages 68-69). Thus, the mouse xenograft model exhibits at least some of the clinical symptoms found in human IBC. In producing animal models comprising a human IBC xenograft, the teachings of the specification are limited to the production of xenografts in immunodeficient mice. While the specification contemplates that other host animals could be used to produce an IBC xenograft model, no specific guidance is offered. The claims cover the use of any immunocompromised host animal, including sheep, pig, and nonhuman primates, but the specification does not provide specific guidance for the use of other appropriate immunocompromised animals beyond mice for the implantation of human tumor cells.

State of the prior art and level of predictability in the art. The specification fails to provide an enabling disclosure for the use of animals other than mice in producing the claimed animal model, because the phenotype of a xenograft model is unpredictable and the specification does not teach other appropriate immunocompromised host animals. The use of a xenograft model as an actual disease model is dependent upon it having an appropriate phenotype. An appropriate phenotype is one that accurately reflects or mimics at least some of the clinical symptoms of human IBC. Otherwise, the animal is not a "model" of anything. The usefulness of a xenograft model is dependent upon it modeling disease characteristics. The specification does not teach how to use an animal model that does not exhibit a phenotype that correlates with human IBC.

The prior art teaches that the phenotype of a xenograft animal model is unpredictable (see Gura, 1997). Gura teaches that xenograft tumors often don't behave like naturally occurring tumors in humans (page 1041, column 2, paragraph 3). Thus, the skilled artisan cannot know *a priori* whether or not the

clinical symptoms observed in the tumor model will correlate with clinical symptoms of the disease. The instant claims cover a wide variety of animal species, including sheep, pig, and nonhuman primates. However, given the unpredictability of phenotype in xenograft model systems, even if immunocompromised host animals were available in other species, the skilled artisan would not know which species would generate a useful model phenotype upon implantation of the MARY-X cell line or a similar cell line. Furthermore, the prior art does not teach appropriate immunocompromised hosts in species other than mice. As the Gura reference discloses, only immunodeficient mice were used for producing xenograft cancer models. The prior art does not disclose appropriate immunocompromised nonhuman primates, sheep, pigs, or other species that could be used to produce the claimed invention.

The purpose of the claimed animal model is to model the inflammatory phenotype. The phenotype of the disclosed mouse xenograft model correlates with some symptoms of human IBC. The instant specification discloses that the observed clinical symptoms observed in the mouse model include (1) bright red skin overlying the tumor and (2) lymphovascular invasion (lymphovascular channels filled with tumor emboli). Thus, although the mouse xenograft model is a useful model system, given the unpredictability in the art of xenograft tumor models, extending the claimed invention beyond mice would require undue experimentation.

In the absence of specific guidance, one skilled in the art would not know how to prepare an IBC xenograft model in an immunocompromised host animal other than a mouse. Given the state of the art, preparing appropriate animal models having a phenotype that correlates with IBC in species other than mice requires undue experimentation.

Relative level of skill of those in the art and quantity of experimentation necessary. Although the level of skill in the art is high, given the high degree of unpredictability in the art of cancer models, the skilled artisan would be required to engage in intensive investigation, rather than routine experimentation to prepare xenografts in species other than mice, such that the xenograft phenotype correlates with the human IBC phenotype. In view of the quantity of experimentation necessary to first

produce appropriate immunocompromised animals across a variety of species suitable for implantation of human graft material and then investigate the clinical phenotype produced in the animal, the unpredictability of phenotype in generating cancer models, the limited working examples, and the limited guidance in the specification, undue experimentation would have been required for one skilled in the art to make and use the claimed compositions and methods.

Claims 6-8 are included in the enablement rejection because they use the term "xenograft" and therefore cover tissue that has been passaged through an animal, for the reasons discussed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is directed to a method of generating the xenograft of Claim 1, by obtaining a breast sample from a patient, identifying cells in the sample as an inflammatory carcinoma exhibiting florid invasion of dermal lymphatics, implanting the sample into an immunocompromised host, and identifying the xenograft growing in the immunocompromised host. However, Claim 1 recites that the xenograft does not express estrogen receptor and progesterone receptor, and does express p53, EGFR, MUC1, and E-cadherin. Thus, although the preamble of Claim 9 recites "a method of generating the xenograft of claim 1", the actual steps do not result in a xenograft having the expression profile recited in Claim 1. Thus, the preamble is in conflict with the body of the claim.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a selection step for identifying and obtaining IBC cells that exhibit the expression profile recited in Claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

Claims 1-12, 28, 29, and 50-52 are rejected under 35 U.S.C. 102(a) as being anticipated by Shao et al. (March 1999, FASEB Journal 13 (4 Part 1): pA187).

The reference discloses a human inflammatory breast carcinoma xenograft model in SCID/nude mice. In particular, the MARY-X cell line is disclosed. The reference discloses that MARY-X grows exclusively within prominent murine lymphovascular spaces. Erythema of the skin overlying the murine tumor was noted. The disclosed MARY-X cell line is ER, PR, Her-2/neu negative and p53, EGFR positive. The xenograft model is said to be useful for studying the step of intravasation. Thus, the reference discloses the claimed xenograft, animal model, method of making the xenograft, and method of using the xenograft.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER